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STRUCTURE FILE UPDATES:    5 JUN 2007  HIGHEST RN 936615-27-9
DICTIONARY FILE UPDATES:   5 JUN 2007  HIGHEST RN 936615-27-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

  Please note that search-term pricing does apply when
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predicted properties as well as tags indicating availability of
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on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

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L15             STR
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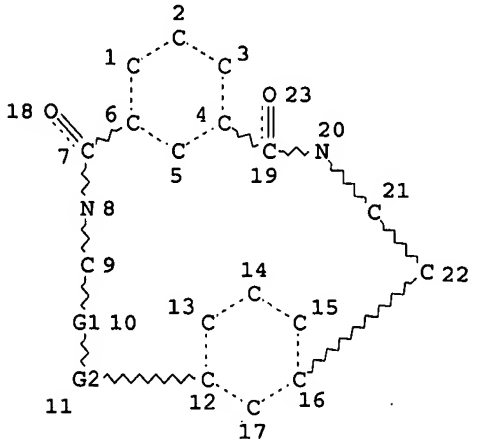


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VAR G2=O/S
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  23

STEREO ATTRIBUTES: NONE
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100.0% PROCESSED   25388 ITERATIONS                    35 ANSWERS
SEARCH TIME: 00.00.01


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FILE 'HCAPLUS' ENTERED AT 14:16:47 ON 06 JUN 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 6 Jun 2007 VOL 146 ISS 24
FILE LAST UPDATED: 5 Jun 2007 (20070605/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d bib abs hitstr retable l13

L13 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:610069 HCAPLUS
DN 141:140475
TI Preparation of macrocyclic β-secretase inhibitors for treatment of
Alzheimer's disease
IN Coburn, Craig A.; Stachel, Shawn J.; Vacca, Joseph P.
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO2004062625	A2	20040729	2004WO-US00085	20040102
	WO2004062625	A3	20050331		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ				
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	CA---2512111	A1	20040729	2004CA-2512111	20040102
	EP---1583750	A2	20051012	2004EP-0700071	20040102
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP2006515881	T	20060608	2006JP-0500780	20040102
	US2006058278	A1	20060316	2005US-0541476	20050706
PRAI	2003US-438630P	P	20030107		
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OS MARPAT 141:140475
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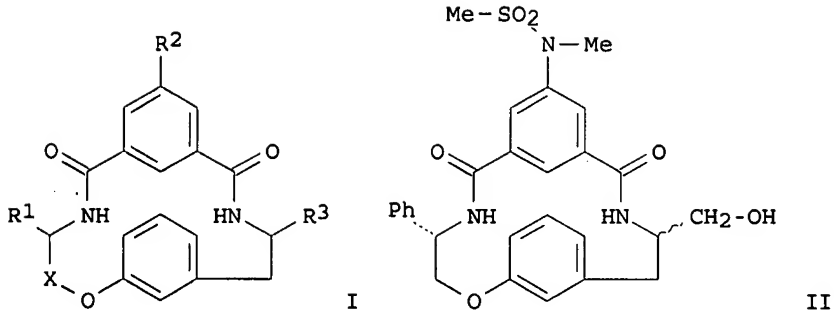


I II

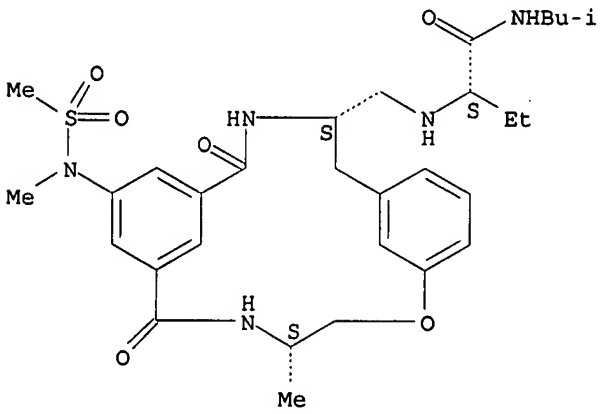
AB Macrocycles of formula I [R1 = H, alkyl, cycloalkyl, (substituted) Ph, etc.; R2 = H, alkyl-SO2N(alkyl), CN, halo, etc.; R3 = CH2OH, CHO, acyl, CH2NH2, CONH2, etc.; X = (CH2)m; m = 1-4] are prepared which are inhibitors of the β-secretase enzyme and are useful in the treatment or prevention of diseases in which β-secretase is involved, such as Alzheimer's disease. The invention is also directed to pharmaceutical compns. comprising these compds. and the use of these compds. and compns. in the prevention or treatment of such diseases in which β-secretase is involved. Thus, II was prepared in several steps from dibenzyl 5-aminoisophthalate, dl-meta-tyrosine and Boc-L-phenylglycinol. The compds. had IC50 values from about 1 nM to 1 μM against β-secretase.

IT **725725-36-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic β-secretase inhibitors for treatment of Alzheimer's disease)

RN 725725-36-0 HCAPLUS

CN Butanamide, 2-[[[(4S,13S)-13-methyl-18-[methyl(methylsulfonyl)amino]-2,15-dioxo-11-oxa-3,14-diazatricyclo[14.3.1.16,10]heneicosa-1(20),6,8,10(21),16,18-hexaen-4-yl]methyl]amino]-N-(2-methylpropyl)-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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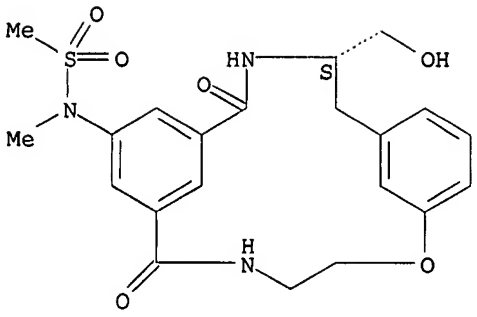
L27 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:1149497 HCAPLUS

DN 146:19371
TI Macrocyclic Inhibitors of β-Secretase: Functional Activity in an Animal Model. [Erratum to document cited in CA145:465146]
AU **Stachel, Shawn J.**; **Coburn, Craig A.**; Sankaranarayanan, Sethu; Price, Eric A.; Wu, Guoxin; Crouthamel, Michelle; Pietrak, Beth L.; Huang, Qian; Lineberger, Janet; Espeseth, Amy S.; Jin, Lixia; Ellis, Joan; Holloway, M. Katharine; Munshi, Sanjeev; Allison, Timothy; Hazuda, Daria; Simon, Adam J.; Graham, Samuel L.; **Vacca, Joseph P.**
CS Department of Medicinal Chemistry, Biological Chemistry, Molecular Systems and Structural Biology, **Merck** Research Laboratories, West Point, PA, 19486, USA
SO Journal of Medicinal Chemistry (2006), 49(24), 7252
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB Guoxin Wu and Michelle Crouthamel were inadvertently omitted from the author list. Their affiliation is the Department of Biol. Chemical, represented by the double dagger symbol in the paper. The correct author list is given.
CC 1-3 (Pharmacology)
Section cross-reference(s): 34
IT **725725-37-1P 725725-38-2P** 847157-19-1P 847157-32-8P
913625-93-1P 913626-00-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(macrocyclic inhibitors of β-secretase and functional activity in an animal model (Erratum))
IT 12135-22-7P, Pearlman's catalyst 50765-19-0P, Methyl-3-Iodo-5-nitrobenzoate 184176-05-4P 217314-45-9P, Methyl 3-amino-5-iodobenzoate
725725-42-8P 725725-51-9P 725725-52-0P **725725-55-3P**
760894-94-8P 847157-47-5P 847157-48-6P 847157-49-7P 847157-50-0P
847157-51-1P 847157-52-2P 847157-53-3P 847157-54-4P 913625-97-5P
913626-02-5P 913626-03-6P 913626-04-7P 913626-05-8P 913626-06-9P
913626-07-0P 913626-08-1P 913626-09-2P 913626-11-6P 913626-12-7P
913626-13-8P 913626-15-0P 913626-16-1P 913626-17-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(macrocyclic inhibitors of β-secretase and functional activity in an animal model (Erratum))
IT **725725-37-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(macrocyclic inhibitors of β-secretase and functional activity in an animal model (Erratum))
RN 725725-37-1 HCAPLUS
CN Methanesulfonamide, N-[(4S)-4-(hydroxymethyl)-2,15-dioxo-11-oxa-3,14-diazatricyclo[14.3.1.16,10]heneicosa-1(20),6,8,10(21),16,18-hexaen-18-yl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



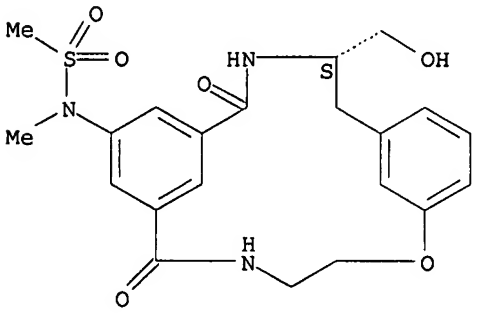
L27 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:908572 HCAPLUS
DN 145:465146
TI Macrocyclic Inhibitors of β-Secretase: Functional Activity in an Animal Model
AU **Stachel, Shawn J.**; **Coburn, Craig A.**; Sankaranarayanan, Sethu; Price, Eric A.; Pietrak, Beth L.; Huang, Qian; Lineberger, Janet; Espeseth, Amy S.; Jin, Lixia; Ellis, Joan; Holloway, M. Katharine; Munshi, Sanjeev; Allison, Timothy; Hazuda, Daria; Simon, Adam J.; Graham, Samuel L.; **Vacca, Joseph P.**
CS Department of Medicinal Chemistry, Biological Chemistry, Molecular Systems and Structural Biology, **Merck** Research Laboratories, West Point, PA, 19486, USA
SO Journal of Medicinal Chemistry (2006), 49(21), 6147-6150
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB A macrocyclic inhibitor of β-secretase was designed by covalently crosslinking the P1 and P3 side chains of an isophthalamide-based inhibitor. Macrocyclization resulted in significantly improved potency and phys. properties when compared to the initial lead structures. More importantly, these macrocyclic inhibitors also displayed in vivo amyloid lowering when dosed in a murine model.
CC 1-3 (Pharmacology)
Section cross-reference(s): 34
IT **725725-37-1P** **725725-38-2P** 847157-19-1P 847157-32-8P 913625-93-1P 913626-00-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(macrocyclic inhibitors of β-secretase and functional activity in an animal model)
IT 12135-22-7P, Pearlman's catalyst 50765-19-0P, Methyl-3-Iodo-5-nitrobenzoate 184176-05-4P 217314-45-9P, Methyl 3-amino-5-iodobenzoate 725725-42-8P 725725-51-9P 725725-52-0P 725725-53-1P **725725-55-3P** 760894-94-8P 847157-47-5P 847157-48-6P 847157-49-7P 847157-50-0P 847157-51-1P 847157-52-2P 847157-53-3P 847157-54-4P 913625-97-5P 913626-02-5P 913626-03-6P 913626-04-7P 913626-05-8P 913626-06-9P 913626-07-0P 913626-08-1P 913626-09-2P 913626-11-6P 913626-12-7P 913626-13-8P 913626-15-0P 913626-16-1P 913626-17-2P 928823-83-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(macrocyclic inhibitors of β-secretase and functional activity in an animal model)
IT **725725-37-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(macrocyclic inhibitors of β-secretase and functional activity in an animal model)

RN 725725-37-1 HCAPLUS

CN Methanesulfonamide, N-[(4S)-4-(hydroxymethyl)-2,15-dioxo-11-oxa-3,14-diazatricyclo[14.3.1.16,10]heneicosa-1(20),6,8,10(21),16,18-hexaen-18-yl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Beher, D	2005	14	1385	Expert Opin Invest D	HCAPLUS
Best, B	2005	313	902	Pharmacol Exp Ther	
Brady, S	2004	14	601	Bioorg Med Chem Lett	HCAPLUS
Cai, H	2001	4	233	Nat Neurosci	HCAPLUS
Coburn, C	2006	16	3635	Bioorg Med Chem Lett	HCAPLUS
Goate, A	1991	349	523	Nature	
Hannessian, S	2006	49	4544	J Med Chem	
Hardy, J	1997	349	704	Proc Natl Acad Sci U	
Hu, X	2004	47	4941	J Med Chem	HCAPLUS
Lamb, B	1993	5	22	Nat Genet	HCAPLUS
Lamb, B	1993	5	22	Nature Genetics	HCAPLUS
Milano, J	2004	82	341	Toxicol Sci	HCAPLUS
Roberds, S	2001	10	1317	Hum Mol Genet	HCAPLUS
Rojo, I	2006	16	191	Bioorg Med Chem Lett	HCAPLUS
Sankaranarayanan, S	2006			10th International c	
Savage, M	1998	18	1743	J Neurosci	HCAPLUS
Scholl, M	1999	1	953	Org Lett	HCAPLUS
Searfoss, G	2003	278	46107	J Biol Chem	HCAPLUS
Selkoe, D	1996	271	18295	J Biol Chem	HCAPLUS
Selkoe, D	1999	399A	23	Nature	
Simon, A	2005			2005 AD/PD meeting	
Sinha, S	1999	96	11049	Proc Natl Acad Sci U	HCAPLUS
Stachel, S	2006	16	641	Bioorg Med Chem Lett	HCAPLUS
Stachel, S	2004	47	6117	J Med Chem	
Stachel, S	2004	47	6447	J Med Chem	HCAPLUS
Thompson, L	2005	11	3383	Curr Pharm Des	HCAPLUS
Tilley, J	1991	34	1125	J Med Chem	HCAPLUS
Tsantrizos, Y	2003	42	1356	Angew Chem, Int Ed	HCAPLUS

L27 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2007 ACS on STN

AN 2004:610069 HCAPLUS

DN 141:140475

TI Preparation of macrocyclic β-secretase inhibitors for treatment of Alzheimer's disease

IN **Coburn, Craig A.; Stachel, Shawn J.; Vacca, Joseph P.**

PA **Merck** & Co., Inc., USA

SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO2004062625	A2	20040729	2004WO-US00085	20040102 <--
	WO2004062625	A3	20050331		
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	CA---2512111	A1	20040729	2004CA-2512111	20040102 <--
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OS MARPAT 141:140475
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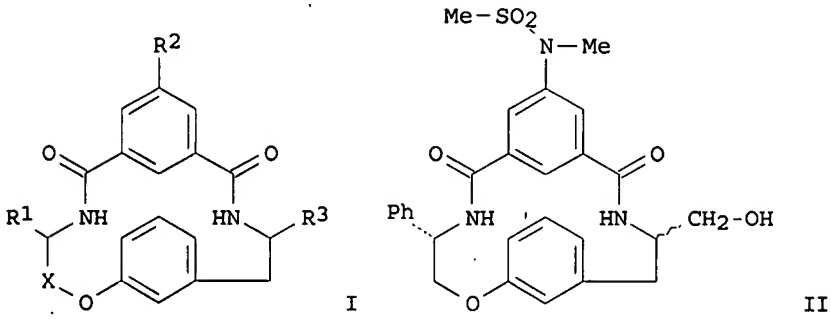

AB Macrocycles of formula I [R1 = H, alkyl, cycloalkyl, (substituted) Ph, etc.; R2 = H, alkyl-SO2N(alkyl), CN, halo, etc.; R3 = CH2OH, CHO, acyl, CH2NH2, CONH2, etc.; X = (CH2)m; m = 1-4] are prepared which are inhibitors of the β-secretase enzyme and are useful in the treatment or prevention of diseases in which β-secretase is involved, such as Alzheimer's disease. The invention is also directed to pharmaceutical compns. comprising these compds. and the use of these compds. and compns. in the prevention or treatment of such diseases in which β-secretase is involved. Thus, II was prepared in several steps from dibenzyl 5-aminoisophthalate, dl-meta-tyrosine and Boc-L-phenylglycinol. The compds. had IC50 values from about 1 nM to 1 μM against β-secretase.

IC ICM A61K
CC 28-23 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
IT **725725-35-9P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of macrocyclic β-secretase inhibitors for treatment of Alzheimer's disease)
IT **725725-31-5P 725725-32-6P 725725-33-7P 725725-34-8P 725725-36-0P 725725-37-1P 725725-38-2P 725725-39-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

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L11            2 L10 AND NRRS>=3
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L19           12 L18 AND L8

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L22            0 L18

     FILE 'USPATFULL, USPAT2' ENTERED AT 14:13:46 ON 06 JUN 2007
L23            1 L18

     FILE 'MEDLINE' ENTERED AT 14:14:08 ON 06 JUN 2007
L24            0 L18

     FILE 'EMBASE' ENTERED AT 14:14:12 ON 06 JUN 2007
L25            0 L18

     FILE 'HCAPLUS' ENTERED AT 14:14:52 ON 06 JUN 2007
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L27            3 L26 AND L1-6

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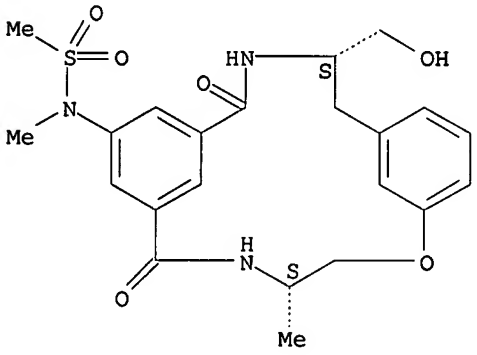
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic β-secretase inhibitors for treatment of Alzheimer's disease)

IT 34260-70-3P 725725-40-6P 725725-41-7P 725725-42-8P 725725-43-9P
725725-44-0P 725725-46-2P 725725-47-3P 725725-48-4P
725725-49-5P 725725-50-8P 725725-51-9P 725725-52-0P
725725-53-1P 725725-54-2P **725725-55-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic β-secretase inhibitors for treatment of Alzheimer's disease)

IT **725725-35-9P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of macrocyclic β-secretase inhibitors for treatment of Alzheimer's disease)

RN 725725-35-9 HCAPLUS
CN Methanesulfonamide, N-[(4S,13S)-4-(hydroxymethyl)-13-methyl-2,15-dioxo-11-oxa-3,14-diazatricyclo[14.3.1.16,10]heneicosa-1(20),6,8,10(21),16,18-hexaen-18-yl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L3 71 E3-5
E STACHEL S/AU
L4 57 E3-4,E8-10
E VACCA J/AU
L5 193 E3,E6,E9-14
L6 34202 MERCK/CS,PA

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FILE 'HCAPLUS' ENTERED AT 13:39:45 ON 06 JUN 2007
L7 TRA L1 1- RN : 36 TERMS

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L8 36 SEA L7

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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